Motivational reserve: Motivation-related occupational abilities and risk of mild cognitive impairment and Alzheimer disease

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Abstract: Midlife motivational abilities, that is, skills to initiate and persevere in the implementation of goals, have been related to mental and physical health, but their association with risk of mild cognitive impairment (MCI) and Alzheimer's disease (AD) has not yet been directly investigated. This relation was examined with data from the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). A total of 3,327 nondemented participants (50.3% of a randomly selected sample) aged 75-89 years were recruited in primary care and followed up twice (after 1.5 and 3 years). Motivation-related occupational abilities were estimated on the basis of the main occupation (assessed at follow-up II) using the Occupational Information Network (O* NET) database, which provides detailed information on worker characteristics and abilities. Cox proportional hazards models were used to evaluate the relative risk of developing MCI and AD in relation to motivation-related occupational abilities, adjusting for various covariates. Over the 3 years of follow-up, 15.2% participants developed MCI and 3.0% developed AD. In a fully adjusted model, motivation-related occupational abilities were found to be associated with a reduced risk of MCI (HR: 0.77; 95% CI: 0.64-0.92). Motivation-related occupational abilities were associated with reduced risk of AD in ApoE 4 carriers (HR: 0.48; CI: 0.25-0.91), but not in noncarriers (HR: 0.99; CI: 0.65-1.53). These results suggest that midlife motivational abilities are associated with reduced risk of MCI in general and with reduced risk of AD in ApoE 4 carriers. Revealing the mechanisms underlying this association may inform novel prevention strategies for decelerating cognitive decline in old age. (PsycINFO Database Record (c) 2011 APA, all rights reserved).

DOI: https://doi.org/10.1037/a0025117

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Accepted by Psychology and Aging

Abstract

Midlife motivational abilities, i.e., skills to initiate and persevere in the implementation of goals, have been related to mental and physical health, but their association with risk of mild cognitive impairment (MCI) and Alzheimer disease (AD) has not yet been directly investigated. This relation was examined with data from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). A total of 3,327 non-demented participants (50.3% of a randomly selected sample) aged 75–89 years were recruited in primary care and followed up twice (after 1.5 and 3 years). Motivation-related occupational abilities were estimated on the basis of the main occupation (assessed at follow-up II) using the Occupational Information Network (O*NET) database, which provides detailed information on worker characteristics and abilities. Cox proportional hazards models were used to evaluate the relative risk of developing MCI and AD in relation to motivation-related occupational abilities, adjusting for various covariates. Over the 3 years of follow-up, 15.2% participants developed MCI and 3.0% developed AD. In a fully adjusted model, motivation-related occupational abilities were found to be associated with a reduced risk of MCI (HR: 0.77; 95% CI: 0.64–0.92). Motivation-related occupational abilities were associated with reduced risk of AD in ApoE ε4 carriers (HR: 0.48; CI: 0.25–0.91), but not in non-carriers (HR: 0.99; CI: 0.65–1.53). These results suggest that midlife motivational abilities are associated with reduced risk of MCI in general and with reduced risk of AD in ApoE ε4 carriers. Revealing the mechanisms underlying this association may inform novel prevention strategies for decelerating cognitive decline in old age.

Key words: Motivation, self-regulation, Alzheimer disease, dementia, mild cognitive impairment.

Word counts main text: 6148

Motivational Reserve: Motivation-Related Occupational Abilities and Risk of Mild Cognitive Impairment and Alzheimer Disease

The term "motivational abilities" refers to a set of skills that are important variables in the implementation of personal goals: the skills of motivation regulation (motivating oneself to persevere), decision regulation (quickly coming to a self-congruent decision), activation regulation (readying oneself to act), and self-efficacy (the belief in being able to bring the intended behavior to a successful conclusion despite difficulties) (Kuhl & Fuhrmann, 1998). Empirically, the skills of action planning and goal orientation have been shown to capture what is meant by these four theoretically derived skills (Forstmeier & Maercker, 2008). Without these motivational abilities, an individual would be unable to persevere with or resume difficult goals. Motivational abilities are incorporated in modern health models (Schwarzer et al., 2007) and have recently been proposed to play a role in brain health (Forstmeier & Maercker, 2008). In the past decade, research has explored the relation of motivational abilities and various health outcomes. Most studies have focused on the prediction of psychiatric disorders such as depression (Rholes, Michas, & Shroff, 1989), anxiety disorders (Casey, Oei, & Newcombe, 2004), and general wellbeing (Kruglanski et al., 2000; Luszczynska, Gutiérrez-Doña, & Schwarzer, 2005; Tangney, Baumeister, & Boone, 2004). Others have explored the prediction of pain control (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1987), health status in chronic diseases (Riazi, Thompson, & Hobart, 2004), or recovery from somatic diseases (Schröder, Schwarzer, & Konertz, 1998). Motivational abilities are also relevant in coping with stress (Beckmann & Kellmann, 2004). The findings of these studies have led to the general conclusion that motivational abilities help individuals to remain mentally and physically healthy.

However, few studies have explored the relation of motivational abilities or related constructs to cognitive decline and dementia (Forstmeier & Maercker, 2008; Schooler,

Mulatu, & Oates, 2004; Wilson, Schneider, Arnold, Bienias, & Bennett, 2007). No prospective study has directly investigated the relation of midlife motivational abilities to risk of MCI and AD. We have recently proposed the assumption that exercising motivational abilities throughout life increases the number of synaptic connections and strengthens existing pathways, leading to the more efficient use of relevant brain networks and to the compensation of disrupted networks (Forstmeier & Maercker, 2008). This idea is in line with the brain reserve hypothesis, which "refers to the ability of the brain to tolerate the pathology of age- and disease-related changes without obvious clinical evidence" (Fratiglioni & Wang, 2007, p. 12) and its associated assumption that behavioral and mental training throughout life leads to a more efficient use of brain networks and compensation of disrupted networks and, in the long run, delays the onset of dementia (Fratiglioni & Wang, 2007; Valenzuela & Sachdev, 2006). In our model of brain reserve, motivational (Forstmeier & Maercker, 2008), cognitive (Stern, 2006), physical (Podewils et al., 2005), and social activities (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000) contribute to brain reserve. Motivational reserve (MR) implies a set of motivational abilities that provide the individual with resilience to neuropathological damage and thus represent one form of brain reserve. The influence of motivational abilities on the brain may be due to their direct effect on neuronal networks in brain areas involved in motivational processes (mainly prefrontal cortex, nucleus accumbens, and the amygdala) (Cardinal, Parkinson, Hall, & Everitt, 2002; Kalivas & Volkow, 2005) or due to indirect effects on mediating processes. For example, motivational abilities might facilitate mental training and social activities throughout life and be important in establishing a "cognitive reserve" (Stern, 2006). Furthermore, the association of motivational abilities with the personality construct of conscientiousness might account for the possible effect on brain structures (Wilson, Schneider, Arnold, Bienias, & Bennett, 2007).

We tested the hypothesized association between motivation-related occupational abilities and risk of MCI and AD with data from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe), a general practice-based prospective longitudinal study on risk factors for MCI and dementia in the elderly (Luck et al., 2007). In our analyses, we also considered possible confounding variables that may explain the potential association between motivational abilities and risk of MCI and AD. A subordinate hypothesis is that the association of motivation-related occupational abilities with risk of AD is higher in ApoE4 carriers than in non-carriers because ApoE ε4 carriers are more susceptible to risk factors associated with lifestyle than are non-carriers (Kivipelto et al., 2008).

Method

Study Sample and Design

The study sample was derived from the AgeCoDe study conducted within the framework of the German Competence Network on Degenerative Dementia. Participants were recruited by their general practitioners (GPs) at six centers in 2003 and 2004. Inclusion criteria for patients were age 75 years and over, absence of dementia (as judged by the GP), and at least one contact with the GP in the last 12 months. Exclusion criteria were consultations only through home visits, residence in a nursing home, severe illness expected by the GP to be fatal within 3 months, insufficient knowledge of German, deafness or blindness, lack of ability to consent, and not being a regular patient of the participating practice. Follow-up I and II examinations were conducted on average 1.5 and 3 years after the interview at study entry. Information on sampling frame, eligible participants, and respondents is provided in Figure 1. Individuals with AD or any other dementia at study entry were excluded from the analysis. In addition, individuals with MCI at study entry were excluded from the analysis to predict risk of MCI. Of the randomly selected sample (n =

6,619), 3,327 (50.3%) completed evaluation; 2,478 (74.5%) of them survived to follow-up II, 2,368 (71.2%) were included for calculation of AD incidence (110 were excluded because of dementia at baseline, age of < 75 years at baseline, or incomplete data), and 2,061 (61.9%) were included for calculation of MCI incidence (an additional of 336 were excluded because of MCI at baseline or MCI indeterminable). The protocol was approved by the ethics committees of all participating sites.

Please insert Figure 1 about here

Neuropsychological and Clinical Evaluation

Structured clinical interviews were conducted by trained physicians and psychologists during visits to the participants' homes. Neuropsychological assessment was based on the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia of Other Etiology according to DSM-III-R, DSM-IV and ICD-10 (SIDAM) (Zaudig & Hiller, 1996). The SIDAM consists of a neuropsychological test battery and a section for clinical evaluation and diagnosis tapping sociodemographic characteristics as well as potential risk factors for cognitive impairment and dementia, and including a 14-item scale assessing activities of daily living (ADL). The SIDAM neuropsychological test battery consists of 55 items (SIDAM cognitive score, SISCO), including the 30 items of the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) and further 25 items that cover verbal working memory, long-term memory, orientation, intellectual abilities, calculation, constructional abilities, and language. The working memory scale consists of five items, including repeating words and one sentence, as well as digit span backward. The Hachinski Rosen-Scale, an empirical scale for the differentiation between degenerative and vascular dementias, is also included (Hachinski et al., 1975). Age-, sex-, and education-specific reference values for the SISCO are available for the German population (Busse et al.,

2002). The SIDAM has high overall test–retest reliability, on the diagnostic as well as on the item level (Zaudig et al., 1991).

In addition, the semantic verbal fluency test (animal naming task) and the verbal memory test (Word List Memory, Word List Recall, and Word List Recognition) of the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) were administered (Morris et al., 1989).

The SIDAM interview, medical history as well as depressive symptoms were obtained at study entry, follow-up I and II. Sociodemographic variables and blood sample for testing for ApoE status were collected at study entry. Lifetime depression as well as cognitive and physical activity was assessed at follow-up I. Occupational history and prevalence of depression since last follow-up were assessed at follow-up II.

Definition of Cases

Incident cases of AD were defined as those participants who developed AD from study entry to follow-up II. Clinical dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994). A diagnosis of Alzheimer's disease required gradual onset and progressive deterioration of cognitive functioning and exclusion of all other specific causes of dementia. Our clinical diagnosis of Alzheimer's disease corresponds to the diagnosis of "probable Alzheimer's disease" according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Vascular dementia diagnosis was guided by the NINDS-AIREN criteria, i.e. evidence of cerebrovascular events (based on the Hachinski scale and the patient's medical history) and a temporal relationship between the cerebrovascular event and the occurrence of cognitive decline (Roman et al., 1993). Mixed dementia was diagnosed when individuals meet inclusion criteria for AD and

were also judged to have cognitive impairment due to vascular dementia. Cases of AD and mixed dementia were combined for all analyses. All diagnoses were made in consensus conferences attended by the interviewer and experienced geriatric psychiatrists or geriatricians.

MCI cases were defined according to the consensus criteria proposed by the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004). These criteria include: (1) absence of dementia according to DSM-IV or ICD-10, (2) self- or informant-reported cognitive decline, (3) impairment on cognitive tasks, and (4) preserved ADL or only minimal impairment in complex instrumental functions. The following procedures were used to assess these criteria. Dementia according to DSM-IV was excluded. Subjective memory complaints were assessed by the question: "Do you feel that your memory has become poorer?" Objective cognitive impairment was defined in terms of the SISCO score, based on the German age-, sex- and education-adjusted normative database (Busse et al., 2002). A score of 1 standard deviation (SD) below the mean was defined as impairment. ADL was assessed by the SIDAM-ADL scale, with a score of 2 or higher being taken to reflect ADL impairment (Zaudig & Hiller, 1996).

Assessment of Motivation- and Cognition-Related Occupational Abilities

The main predictor in this study was motivation-related occupational abilities, estimated by reference to a sample of Occupational Information Network (O*NET) variables on the basis of each participant's main occupation. Cognition-related occupational abilities, estimated by the same procedure, were used as a covariate in the analyses.

The O*NET is the official occupational classification system of the US Department of Labor (Peterson, Mumford, Borman, Jeanneret, & Fleishman, 1999). It consists of a hierarchically structured lexicon of about 1,100 occupations and a large database of associated work and worker characteristics—the result of an ongoing large-scale research

project conducted over recent decades. The database includes empirically collected data on the abilities and skills needed in each occupation. In the O*NET data collection program, questionnaires were used to assess samples of workers in each job. Each new version of the O*NET represents an update of these data. Version 12.0, which is used in this study, is based on samples of n = 20 to 70 incumbents per occupation. Most O*NET variables relating to skills, abilities, and work activities have been shown to have high interrater reliability and to be valid (high correlations with expert ratings) (Peterson et al., 1999).

We used a three-step procedure to estimate participants' motivation- and cognition-related occupational abilities. First, participants and, whenever possible, their informants were asked to name the occupations they held (a) in the first job they held for at least 1 year after finishing education, (b) in their longest held jobs, and (c) in the last job of their professional life. For each job, data were collected on duration, job title, and major activities and duties. Only data on the main (longest) occupation were processed any further.

Second, O*NET occupational codes were assigned on the basis of the main occupation. Information on participants' major activities and duties is crucial for their coding to O*NET occupations. The coders compared the activities and duties the participant indicated with those provided for each O*NET occupation. The occupation exhibiting the best match was selected. The O*NET procedure is thus also largely applicable to German occupations because coding is not only based on the job title but also on the activities and duties in this job. Each participant's occupational information was coded independently by two coders; any coding differences were reconciled in discussion with the first author. In cases of disagreement, the participant's answers and the O*NET job descriptions were reexamined and the coding was discussed until a majority consensus was reached. Initial interrater agreement was 86% at the highest level of aggregation (2 digits), 74% at the second highest level (3 digits), and 66% at the lowest level of the detailed O*NET occupations (8

digits). Participants who had been housewives for the longest period were classified according to their second-longest held job; 126 participants who had been housewives all their lives were coded as "personal and home care aides."

Third, two motivational and four cognitive O*NET variable values belonging to this O*NET occupation were assigned to the participant. The selection of these variables is detailed elsewhere (Forstmeier & Maercker, 2008). In short, variables were selected in a sample of non-demented elderly people on the basis of (a) their content validity and (b) their correlations with self-reported motivational abilities and a measure of crystallized (verbal) intelligence. Two variables were highly significantly associated with self-reported motivational abilities but not with intelligence: goal orientation (item 4.A.2.b.6; "developing specific goals and plans to prioritize, organize, and accomplish your work"; M (SD) in the present sample 3.92 (1.06), range = 5.74) and action planning (4.A.1.b.3; "determining time, costs, resources, or materials needed to perform a work activity"; M (SD) = 2.19 (0.80), range = 4.43). Four variables were highly significantly correlated with intelligence but not with self-reported motivational abilities: selective attention (1.A.1.g.1; "ability to concentrate on a task over a period of time without being distracted"; M (SD) = 2.71 (0.39), range = 3.13), recognizing problems (1.A.1.b.3; "ability to tell when something is wrong or is likely to go wrong"; M (SD) = 3.36 (0.61), range = 4.10), assessing performance (2.A.2.d; "assessing performance of yourself, other individuals, or organizations to make improvements"; M (SD) = 3.13 (0.70), range = 2.92), and social perceptiveness (2.B.1.a; "being aware of others' reactions and understanding why they react as they do"; M (SD) = 3.68 (0.91), range = 6.70).

A composite for motivation-related occupational abilities was constructed based on the *z*-standardized scores of goal orientation and action planning. Likewise, a composite for cognition-related occupational abilities was constructed based on the *z*-standardized scores of the four cognitive variables. Internal consistency (alpha) was 0.70 for the O*NET

motivational abilities total score and 0.79 for the O*NET cognitive abilities total score in the present study. The two total scores were used in the following analyses.

Assessment of Other Covariates

Education. Participants reported their highest level of schooling (i.e., vocational track, intermediate track, academic track, other, no school leaving certificate) and their highest level of professional training (vocational training, technical college, university of applied science, university, other, no professional training). We then constructed a three-category variable for educational level (low, intermediate, high), based on the revised version of the international CASMIN educational classification (Brauns & Steinmann, 1999). In addition, total years of formal education were calculated from the answers to these two questions.

Cognitive and physical activity. At follow-up I, participants were interviewed on the frequency of their participation in 7 cognitive activities (doing crossword puzzles, doing memory training, playing board games or cards, reading books or newspapers, writing for pleasure, playing musical instruments, and social engagement in a formal group, e.g., a club or church) and 7 physical activities (bicycling, walking for exercise, swimming, doing gymnastics, doing housework, babysitting, and other sports), as adapted from previous research (Verghese et al., 2003). Participants reported the frequency of participation on a 5-point scale, with 4 indicating "daily," 3 "several days per week," 2 "once weekly," 1 "less than once weekly," and 0 "never." Two mean item scores for cognitive and physical activities were used in analyses, as in previous research (Wilson et al., 2002).

Family network. Information on the family network was obtained at study entry by three questions tapping marital status ("married" coded as 1, "single," "divorced," and "widowed" as 0), having siblings ("yes" coded as 1, "no" as 0), and having children ("yes" coded as 1, "no" as 0). The sum of these three dichotomous variables was used as a family network index in the analyses.

Vascular risk factors and vascular diseases. At study entry, the GP of each participant filled in a questionnaire that included questions tapping vascular risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus) and vascular diseases (i.e., myocardial infarction, coronary heart disease, cardiac arrhythmia, stroke). To assess the influence of cumulative vascular risk factors and vascular disease burden on MCI and AD incidence, we calculated two summary scores indicating the participant's vascular risk factor sum (score from 0 to 3) and vascular disease sum (0 to 4), as adapted from previous research (Boyle et al., 2005).

Lifetime depression, depressive symptoms, and minor and major depression. The depression section of the Munich-Composite International Diagnostic Interview (M-CIDI) (Wittchen & Pfister, 1997) was used to assess lifetime depression as well as minor and major depression between follow-up I and II according to DSM-IV and ICD-10 criteria.

Depressive symptoms were assessed by the 15-item version of the Geriatric Depression Scale (GDS) (Yesavage et al., 1983) at study entry, follow-up I and II. The GDS is a depression screening tool with good psychometric properties for German-speaking populations (Wancata, Alexandrowicz, Marquart, Weiss, & Friedrich, 2006).

Apolipoprotein E ε4 Genotyping. For DNA analysis, leukocyte DNA was isolated using the Qiagen blood isolation kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). ApoE genotyping was performed according to standard procedures (Hixson & Vernier, 1990). In the analyses, participants were divided into those with at least one copy of the ε4 allele and those without an ε4 allele. For 87 (3.7%) participants, either DNA was not available or the ApoE genotype could not be determined. Of the remaining participants, 18 (0.8%) were homozygote ApoE4 carriers, 454 (19.9%) were heterozygote ApoE4 carriers, and 1809 (79.3%) did not carry an ApoE4 allele.

Statistical Analyses

The data were collected from the centers via an internet-based remote data entry system into a central ORACLE version 9 database. The statistical analyses were performed with SPSS for Windows, version 17.0. Cox proportional hazards models were used to estimate the relative risk (hazard ratios, HR) and corresponding 95% confidence intervals (CI) of developing MCI and AD in relation to motivation-related occupational abilities. Age, sex, and education were used as covariates in all models. To verify whether the association between motivation-related occupational abilities and MCI or AD development was due to midlife cognitive abilities, cognitive functioning (MMSE) at study entry, physical functioning (ADL) at study entry, cognitive activity, physical activity, family network characteristics, vascular risk factors and vascular diseases, lifetime depression, depressive symptoms at all three time-points (as time-varying variable), minor and major depression, verbal working memory, or ApoE ε4 status, we added these variables to multiple Cox regression models—first separately, and then simultaneously. Sex, education, family network, vascular risk factors, vascular diseases, lifetime depression, and ApoE ε4 status were entered in the models as categorical variables; all other variables were entered as continuous variables. Since motivation-related occupational abilities estimated on the basis of the main occupation did not differ significantly from those estimated on the basis of the first or last occupation, analyses included only motivational abilities based on main occupation.

Results

Sample Characteristics

Over the 3 years of follow-up, 313 (15.2%) participants developed MCI and 71 (3.0%) developed AD. Note that these figures are slightly lower than those previously published for the AgeCoDe study (Jessen et al., 2010), because occupational history was assessed at follow-up II, when some of the MCI and AD cases already had dropped out.

Table 1 shows the characteristics for the total sample and for participants who developed/did not develop MCI or AD. Those who developed MCI or AD were older, more educated, more cognitively impaired, more likely to have an ApoE ε4 allele, and had lower motivation-related occupational abilities scores than those who did not. The distribution of motivational abilities was symmetric (skewness = -0.01, SE = 0.05) and its kurtosis near to that of a normal distribution (kurtosis = -0.49, SE = 0.10).

Please insert Table 1 about here

Motivation-Related Occupational Abilities and Incidence of Mild Cognitive Impairment

When the motivation-related occupational abilities score was used as continuous variable and age, sex, and educational level were controlled (Model 1 in Table 2), the HR of developing MCI was 0.73 (95% CI: 0.65–0.89).

In subsequent analyses, other potential risk factors were controlled (Models 2–9 in Table 2). The occupation-based measure of midlife cognitive abilities showed a moderate correlation with motivation-related occupational abilities ($r = 0.39$, $p < 0.001$; adjusted for age, sex, and education). However, when the analysis was repeated with a term to control for the effect of cognition-related occupational abilities, motivation-related occupational abilities continued to be associated with reduced risk of MCI (HR: 0.76; 95% CI: 0.65–0.89).

Because cognitive and physical functioning at study entry might be associated with risk of MCI (Bennett et al., 2002), the MMSE and the SIDAM-ADL scores were added to the model. There was no essential change in the association of motivation-related occupational abilities with MCI risk in this analysis (HR: 0.80; 95% CI: 0.68–0.94). Working memory might possibly serve as a basis of motivation-related occupational abilities. However, controlling for working memory did not change the association (HR: 0.77; 95% CI: 0.65–0.90).

The effect of motivation-related occupational abilities on risk of cognitive impairment may be mediated by an active life style, by reducing vascular risk factors via better health behaviors, and by preventing depressive syndromes (Forstmeier & Maercker, 2008). Separate models that controlled for frequency of cognitive activity, frequency of physical activity, and family network (HR for motivation-related occupational abilities: 0.75; 95% CI: 0.64–0.88), summary scores of vascular risk factors and vascular diseases (HR: 0.76; 95% CI: 0.65–0.89), lifetime depression (HR: 0.76; 95% CI: 0.64–0.90), depressive symptoms at all time-points (HR: 0.77; 95% CI: 0.65–0.90), or minor or major depression between follow-up I and II (HR: 0.75; 95% CI: 0.64–0.88) showed that the association of motivation-related occupational abilities with risk of MCI persisted.

Because possession of an ApoE4 ε4 allele has been related to risk of AD and may also be associated with risk of MCI (Luck et al., 2007), the analysis was repeated with a term for the ApoE4 allele. Motivation-related occupational abilities continued to be associated with reduced risk of MCI (HR: 0.75; 95% CI: 0.64–0.88). A model including the interaction of ApoE4 ε4 allele and motivational abilities resulted in a similar risk (HR: 0.76; 95% CI: 0.64–0.91).

A final model included all of the covariates from the preceding analyses. In this fully adjusted model, motivation-related occupational abilities continued to be associated with reduced risk of MCI (HR: 0.79; 95% CI: 0.66–0.96). A participant with high motivational abilities (highest tertile) had a 35% lower risk of MCI than a participant with low motivational abilities (lowest tertile) (HR: 0.65; 95% CI: 0.44–0.96).

Please insert Table 2 about here

Motivation-Related Occupational Abilities and Incidence of Alzheimer Disease

The same sequence of analyses was conducted to predict risk of AD (Table 2). In the basic model adjusted for age, sex, and education, the HR of developing AD in relation to

motivation-related occupational abilities was 0.84, but this association was not significant (CI: 0.62–1.14). The association remained non-significant in subsequent analyses controlling for other risk factors (Models 2–12 in Table 2), including the fully adjusted model (HR: 0.90; 95% CI: 0.66–1.59).

ApoE ε4 carriers have been shown to be more vulnerable to lifestyle-related risk factors than non-carriers (Kivipelto et al., 2008). Therefore, we hypothesized that the association of motivation-related occupational abilities with risk of AD would be higher in ApoE4 carriers than in non-carriers. Table 3 presents the HRs and CIs of developing AD by ApoE4 genotype. In the fully adjusted model, the HR of developing AD was 0.48 (CI: 0.25–0.91) in ApoE4 carriers, but 0.99 (CI: 0.65–1.53) in non-carriers. Thus, the association of motivation-related occupational abilities with AD risk was significant only in ApoE4 carriers, and not in non-carriers.

Please insert Table 3 about here

Discussion

We examined the association of motivation-related occupational abilities with incidence of MCI and AD in a sample of nearly 2,500 participants aged 75 and older in a prospective study with follow-up after 3 years. We found that participants with high motivational abilities were 35% less likely to develop MCI than participants with low motivational abilities, even when other potential risk factors were controlled. The association of motivation-related occupational abilities with incidence of AD was less clear. When other potential risk factors were controlled, a higher level of motivation-related occupational abilities was associated with reduced risk of AD in ApoE ε4 carriers, but not in non-carriers. These results suggest that motivational abilities are associated with reduced risk of MCI in general and with reduced risk of AD in ApoE ε4 carriers.

To our knowledge, this is the first study to investigate midlife motivational abilities as a predictor of risk of MCI and AD. In a previous cross-sectional study, we showed that the same occupation-based measure of midlife motivational abilities was associated with lower cognitive function in old age (Forstmeier & Maercker, 2008). Self-directed occupational conditions, which can be assumed to foster motivational abilities, have been found to be associated with increased intellectual functioning 20 years later (Schooler et al., 2004). Conscientiousness, a related construct that can be defined as the tendency to control impulses and to be goal directed, has been found to be associated with a lower risk of MCI and AD in a longitudinal study (Wilson et al., 2007). Internal control, a construct similar to self-efficacy, has been found to correlate with hippocampal volume, suggesting that the association of motivational abilities with cognitive impairment in old age is at least partly attributable to the effect of motivational activities on brain structures (Pruessner et al., 2005).

Possible mechanisms underlying the association

The mechanisms underlying the association of motivation-related occupational abilities with incident MCI and AD remain unclear. Our main hypothesis is that exercising motivational abilities throughout life increases the number of synaptic connections and strengthens existing pathways, leading to the more efficient use of relevant brain networks and to the compensation of disrupted networks (Forstmeier & Maercker, 2008). This idea is in line with the brain reserve hypothesis (Fratiglioni & Wang, 2007; Valenzuela & Sachdev, 2006); the term “motivational reserve” refers to the contribution of lifetime motivational activities to general brain reserve, in addition to cognitive (Stern, 2006), physical (Podewils et al., 2005), and social activities (Fratiglioni et al., 2000). The brain areas primarily involved in motivational processes are the prefrontal cortex (regulating motivational salience and determining intensity of responding), the nucleus accumbens (reward-motivated behavior), and the amygdala (fear-motivated behavior) (Cardinal et al., 2002; Kalivas & Volkow, 2005).

The neuroplastic advantages of people with high motivational abilities may equip them with greater tolerance of neuropathological changes in these areas.

We also proposed that additional factors might mediate the effect of motivational abilities on further brain areas (Forstmeier & Maercker, 2008). In particular, motivational abilities might influence health behaviors, mental training throughout life, and risk of depression. Health behaviors reduce cardiovascular risk factors (Mensink, Ziese, & Kok, 1999) known to be involved in the pathogenesis and progression of AD (Launer, 2002). Motivational abilities are predictors of educational and occupational attainment (Tangney et al., 2004) suggesting that motivational reserve may facilitate mental training throughout life and be important in establishing a "cognitive reserve" (Stern, 2006). Motivational abilities are associated with reduced risk of depression (Rholes et al., 1989) which has been proposed as a risk factor for dementia (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). However, controlling for all of these variables did not alter our findings. Rather, our data suggest that midlife motivational abilities represent a largely independent predictor of cognitive impairment in old age that influences cognitive decline via cardiovascular risk factors, mental training, and risk of depression.

Motivational abilities are also known to be important in modulating stress response (Beckmann & Kellmann, 2004) and might thus reduce the adverse effect of stress on risk of AD. High concentrations of stress hormones have been shown to be associated with impaired cognitive function and hippocampal atrophy in AD (Lupien et al., 1999), and proneness to psychological stress (neuroticism) has been linked to risk of AD (Wilson et al., 2006). We did not include a measure of neuroticism in this study, nor can we test glucocorticosteroid effects as a mediator of the association of motivational abilities with cognition. Further studies are required to test this hypothesis.

Why were motivation-related occupational abilities found to be risk factors for AD only in ApoE ε4 carriers in this sample? We propose one methodological and one theoretical explanation. From a methodological point of view, the statistical power of the study may have been too low to detect a statistically significant association with AD risk. Indeed, there were far fewer AD cases (n = 71) than MCI cases (n = 313) in the present sample. This explanation is supported by the findings that the HRs of developing MCI and AD were exactly the same (0.78) in the fully adjusted model and that the confidence interval for AD risk did not greatly exceed 1.0. If this explanation holds, a sample with more AD cases should result in a different pattern of findings. We will be able to investigate this possibility with the follow-up III data.

From a theoretical point of view, ApoE ε4 carriers may be more vulnerable to environmental factors than non-carriers. Previous studies have found that lifestyle and vascular risk factors increase the risk of AD particularly in ApoE ε4 carriers (Kivipelto et al., 2008). Interestingly, ApoE ε4 not only influences AD, but also other neurological disorders. The common molecular mechanism by which ApoE ε4 contributes to neurodegeneration is that it intensifies the biochemical disturbances that are characteristic of AD, including beta amyloid deposition, tangle formation, neuronal cell death, oxidative stress, synaptic plasticity, and intracellular signaling (Cedazo-Minguez & Cowburn, 2001). We have described the primary mechanism by which midlife motivational abilities are associated with MCI and AD risk in terms of increased neuroplasticity and compensation of neuronal loss, leading to motivational reserve. ApoE ε4 carriers show poor neuronal compensation, which might intensify the detrimental effect of low motivational reserve.

Strengths and limitations

An aspect deserving particular attention is the O*NET-based estimate of midlife motivational abilities. Estimates of premorbid characteristics based on educational and

occupational data (e.g., years of formal education, Stern et al., 1994, or complexity of work activities, Kröger et al., 2008) have a long tradition in dementia research. They are usually applied to estimate premorbid cognitive abilities. The present study was the first to apply the O*NET database on worker skills and characteristics to predict risk of MCI and AD. Although our estimate of motivation-related occupational abilities is not a direct measure, its validity in estimating motivational as opposed to cognitive abilities has previously been demonstrated (Forstmeier & Maercker, 2008). The use of the O*NET in epidemiological research rests on the supposition that O*NET work and worker characteristics collected from a sample of worker (n = 20-70) in each job applies largely to all individuals working in that job. We assume a reciprocal relationship. Individuals with certain motivational and cognitive skills gravitate toward occupations needing these skills. Conversely, working in a job with certain psychological demands for most of one's working life affects one's abilities. Clearly, individuals can be overqualified - in the sense of having skills in excess of those required to perform the tasks associated with the job - or they can be under-qualified. Although both are possible, models of job design and recruitment (Albrecht & Vroman, 2002) and empirical data (Wilk, Desmarais, & Sackett, 1995) assume that exceptions to positive assortative matching are of minor importance. However, one must bear in mind that our measures of motivation- and cognition-related occupational abilities are only estimates based on groups of workers and that they provide only inferential characterizations of a particular individual. Moreover, although the procedure of matching activities and duties in the German occupation with activities and duties in the US occupation reduces problems with the applicability of the US occupational system, it is clear that this measure constitutes only an estimate, which also includes measurement errors.

The strengths of the present study include its large sample size, the multi-site design, and the ability to control for most of the potential risk factors of AD. In contrast to previously

used occupation-based measures, the O*NET-based measure makes it possible to disentangle motivational and cognitive abilities (Forstmeier & Maercker, 2008). The clinical diagnosis of MCI and AD was based on a uniform evaluation and widely accepted criteria applied by experienced clinicians, minimizing the likelihood of diagnostic error.

Some limitations of the study must be taken into consideration. Residents of nursing homes and patients who were unable to attend their GP practice were excluded from the study, resulting in rather conservative estimates of MCI and AD incidence rates. Only about 50% of randomly selected patients consented to participate; thus, a selection bias cannot be excluded. The present cohort is not population-based, however, about 95% of the population in this age group are registered at a GP office (Jessen et al., 2007). Since a chart registry approach was used rather than a waiting room recruitment strategy, the study participants are unselected and can be considered representative for community dwelling elderly. There is the possibility of a differential survival, both from midlife and from study entry. Individuals with high motivation-related occupational abilities might have a higher survival rate, possibly leading to a higher portion of individuals with high motivational ability in this sample. The follow-up period of 3 years is rather short, so subjects that developed MCI or AD from study entry to follow-up might already have been slightly impaired at study entry. However, since the main predictor is motivation-related occupational abilities, the possible slight impairment at study entry does not influence the results significantly.

Not all variables used in the analyses have been collected at all time-points; in particular, occupational history was assessed at follow-up II only. This might have reduced the validity of the assessment of occupational history in the subsample of participants which have developed AD by this time. However, we believe that the validity is acceptable because, whenever possible, the informant was present and contributed to recalling the occupational history, and our experience showed that people with MCI and early AD had no difficulty in

answering the questions (not surprisingly since long-term memories usually remain intact in the early stage of AD). Similarly, although the validity of the CIDI for the diagnosis of lifetime depression has been demonstrated (Reed et al., 2006), the retrospective assessment with people with cognitive impairment might have reduced its validity. We tried to improve the validity by including information by the caregiver, whenever possible.

Our findings regarding the association of motivation-related occupational abilities with reduced risk of MCI and—in ApoE4 carriers—AD, only pertain to our occupation-based measure of motivational abilities. A consequence of the use of this measure is that the present study is not prospective. Although we have argued that the validity of this measure is acceptable, the retrospective nature of this study limits its generalizability and interpretation in terms of causal relationship. A further consequence of this measure is that women's motivational ability might be underrated because in a portion of women, who were housewives most of their lives, occupational coding was based on the second-longest held job. However, analyses without this portion of women didn't change the large picture of results. Other studies using further measures of motivational ability constructs are required to confirm that motivational abilities represent a stable risk factor for cognitive impairment. In addition, our construct of motivational abilities comprises four skills, but the composite, occupation-based measure used in this study precluded investigation of its subcomponents. Furthermore, we did not include pre-existing psychiatric disorders other than depression and substance abuse as covariates in the analyses.

Finally, the mechanisms underlying the association of motivational abilities and risk of cognitive impairment remain unclear. Disentangling the complex association between motivational, cognitive, physical, and social activities, neuronal degeneration, and cognitive impairment is likely to require clinical pathological research, larger epidemiological studies, and evaluation of prevention programs including motivational training (Forstmeier & Rüddel,

2007). Insights into the mechanisms linking motivational abilities to risk of cognitive impairment in old age may lead to new strategies for delaying the onset of AD symptoms.

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This paper reports on data from the longitudinal study “German Study on Ageing, Cognition and Dementia in Primary Care Patients” (AgeCoDe). This research was conducted within the framework of the German Research Network on Dementia (KND) and the German Research Network on Degenerative Dementia (KNDD) and was funded by the German Federal Ministry of Education and Research (grants KND: 01GI0102, 01GI0420, 01GI0422, 01GI0423, 01GI0429, 01GI0431, 01GI0433, 01GI0434; grants KNDD: 01GI0710,

01GI0711, 01GI0712, 01GI0713, 01GI0714, 01GI0715, 01GI0716). The research was also supported by a grant from the Dr. med. Kurt Fries Foundation, Zurich, Switzerland.

We would like to thank all participating patients and their general practitioners (named below) for their generous cooperation:

Hamburg: Gundula Bormann, Winfried Bouché, Doris Fischer-Radizi, Michael Funke, Heike Gatermann, Wolfgang Herzog, Petra Hütter, Stefanie Kavka-Ziegenhagen, Günther Klötzl, Bernd-Uwe Krug, Dietrich Lau, Ursula Linn, Andrea Moritz, Karl-Christian Münter, Detlef Niemann, Klaus Richard-Klein, Walter Schreiber, Ursula Schröder-Höch, Gerhard Schulze, Klaus Stelter, Carl-Otto Stolzenbach, Ljudmila Titova, Klaus Weidner, Otto-Peter Witt, Eckehard Zeigert;

Mannheim: Gerhard Arnold, Veit-Harold Bauer, Werner Besnier, Hanna Böttcher-Schmidt, Hartmut Grella, Gernot Kunzendorf, Ingrid Ludwig, Manfred Mayer, Hubert Mühlig, Arnt Müller, Adolf Noky, Helmut Perleberg, Carsten Rieder, Michael Rosen, Georg Scheer, Michael Schilp, Matthias Schneider, Jürgen Wachter, Brigitte Weingärtner, Hans-Georg Willhauck;

Bonn: Jörg Eimers-Kleene, Klaus Fischer, Maria Goebel-Schlatholt, Peter Gülle, Wolf-Dietrich Honig, Hans Jürgen Kaschell, Hanna Liese, Manfred Marx, Eberhard Prechtel, Heinz-Peter Romberg, Heribert Schützendorf, Annemarie Straimer, Martin Tschoke, Karl-Michael Werner;

Halstenbek: Herrmut Mayen;

Königswinter: Theodor Alfen;

Bad Honnef: Klaus Weckbecker;

Niederkassel: Inge Bürfent;

Alfter-Oedekoven: Johann von Aswege;

Erfstadt-Liblar: Arndt Uhlenbrock;

Windeck-Herchen: Wolf-Rüdiger Weisbach;

Leipzig: Martina Amm, Heinz-Michael Assmann, Horst Bauer, Barbara Bräutigam, Jochen Ebert, Angelika Gabriel, Eva Hager, Gunter Kässner, Ina Lipp, Thomas Lipp, Ute Mühlmann, Gabi Müller, Thomas Paschke, Gabriele Rauchmaul, Ina Schmalbruch, Holger Schmidt, Hans-Christian Taut, Ute Voß, Bettina Winkler, Sabine Ziehbold;

Munich: Eugen Allwein, Guntram Bloß, Peter Dick, Johann Eiber, Lutz-Ingo Fischer, Peter Friedrich, Helga Herbst, Andreas Hofmann, Günther Holthausen, Karl-Friedrich Holtz, Ulf Kahmann, Elke Kirchner, Hans Georg Kirchner, Luitpold Knauer, Andreas Koeppel, Heinz Koschine, Walter Krebs, Franz Kreuzer, Karl Ludwig Maier, Christoph Mohr, Elmar Schmid, Gabriel Schmidt, Johann Thaller;

Haar: Richard Ellersdorfer, Michael Speth;

Dusseldorf: Angela Ackermann, Pauline Berger, Florinela Cupsa, Barbara Damanakis, Klaus-Wolfgang Ebeling, Tim Oliver Flettner, Michael Frenkel, Friederike Ganßauge, Kurt Gillhausen, Hans-Christian Heede, Uwe Hellmessen, Benjamin Hodgson, Bernhard Hoff, Helga Hümmerich, Boguslaw-Marian Korman, Dieter Lüttringhaus, Dirk Matzies, Vladimir Miasnikov, Wolfgang Josef Peters, Birgitt Richter-Polynice, Gerhard Erich Richard Schiller, Ulrich Schott, Andre Schumacher, Harald Siegmund, Winfried Thraen, Roland Matthias Unkelbach, Clemens Wirtz.

Further members of the AgeCoDe study group (German Study on Ageing, Cognition and Dementia in Primary Care Patients): Heinz-Harald Abholz, Matthias C. Angermeyer, Cadja Bachmann, Wolfgang Blank, Michaela Buchwald, Mirjam Colditz, Moritz Daerr, Sandra Eiffländer-Gorfer, Marion Eisele, Angela Fuchs, Sven Heinrich, Frank Jessen, Teresa Kaufeler, Hans-Helmut König, Tobias Luck, Manfred Mayer, Edelgard Mösch, Julia Olbrich, Heinz-Peter Romberg, Anja Rudolph, Melanie Sauder, Britta Schuermann, Jochen Werle, Anja Wollny, Thomas Zimmermann.

Table 1

Characteristics of Participants Who Developed/Did Not Develop Mild Cognitive Impairment (MCI) and Alzheimer Disease (AD)

Characteristic	Total[a]	Unaffected Persons (n = 1748)[a]	Incident MCI (n = 313)[a]	*p*[b]	Unaffected Persons (n = 2297)[a]	Incident AD (n = 71)[a]	*p*[b]
Age, years	79.4 (3.4)	79.3 (3.2)	79.9 (3.6)	.001	79.4 (3.4)	81.0 (3.9)	.000
75–79 years, %	56.3	57.2	51.8	.002	57.0	33.8	.000
80–84 years, %	36.5	37.2	37.4		36.0	52.1	
85–98 years, %	7.1	5.6	10.9		6.9	14.1	
Sex, % Female	65.9	65.7	64.9	.779	65.5	78.9	.019
Education, years	12.1 (2.3)	11.9 (2.1)	12.5 (2.7)	.000	12.1 (2.3)	11.5 (2.2)	.040
Low educational level[c]	60.5	67.5	41.9	.000	60.3	67.6	.405
Moderate educational level[c]	27.8	22.9	38.3		28.0	21.1	
High educational level[c]	11.7	9.6	19.8		11.7	11.7	
Midlife motivational abilities[d]	0.00 (0.9)	0.03 (0.9)	-0.06 (0.9)	.012	0.01 (0.9)	-0.2 (0.9)	.046
Midlife cognitive abilities[d]	-0.00 (0.8)	-0.01 (0.8)	0.003 (0.8)	.782	0.0001 (0.8)	-0.05 (0.7)	.608
Cognitive functioning (MMSE)	27.7 (1.8)	28.0 (1.5)	27.4 (1.8)	.000	27.8 (1.7)	25.8 (2.2)	.000
Physical functioning (ADL)	13.9 (0.4)	13.94 (0.3)	13.88 (0.4)	.009	13.9 (0.3)	13.8 (0.7)	.064
Vascular risk factors[e]	1.5 (0.9)	1.5 (0.9)	1.4 (0.9)	.820	1.4 (0.9)	1.5 (0.9)	.398
Vascular diseases[f]	0.8 (0.9)	0.7 (0.9)	0.9 (1.0)	.041	0.8 (0.9)	0.8 (0.9)	.680
ApoE ε4 allele, %	20.7	19.3	25.2	.019	20.2	35.2	.002

Abbreviations: AD, Alzheimer disease; ADL, activities of daily living; ApoE, apolipoprotein E; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

[a] Unless otherwise specified, data represent mean (SD).

[b] P value of t or χ^2 tests.

[c] Based on the revised version of the international CASMIN educational classification.

[d] Average of *z* scores of O*NET variables.

[e] Mean number of vascular risk factors of a maximum of 3 (i.e., hypertension, hypercholesterolemia, diabetes mellitus).

[f] Mean number of vascular diseases of a maximum of 4 (i.e., myocardial infarction, coronary heart disease, cardiac arrhythmia, stroke).

Table 2

Hazard Ratio (HR) and 95% Confidence Interval (CI) of Developing MCI and AD in Relation to Midlife Motivational Abilities

	MCI (n = 313)		AD (n = 71)		
Model	HR	95% CI	HR	95% CI	Covariates
1	0.73	0.63–0.84	0.84	0.62–1.14	Age, sex, and educational level
2	0.76	0.65–0.89	0.81	0.59–1.11	Basic model: Midlife cognitive abilities, age, sex, and educational level
3	0.80	0.68–0.94	0.89	0.65–1.22	Cognitive functioning (MMSE), physical functioning (ADL) plus basic model
4	0.77	0.65–0.90	0.81	0.59–1.11	Verbal working memory plus basic model
5	0.75	0.64–0.88	0.86	0.63–1.16	Cognitive activity, physical activity, family network plus basic model
6	0.76	0.65–0.89	0.81	0.59–1.11	Vascular risk factors, vascular diseases plus basic model
7	0.76	0.64–0.90	0.77	0.54–1.09	Lifetime depression plus basic model
8	0.77	0.65–0.90	0.84	0.61–1.16	Depressive symptoms at all time-points plus basic model
9	0.75	0.64–0.88	0.89	0.63–1.26	Minor or major depression between follow-up I and II plus basic model
10	0.75	0.64–0.88	0.80	0.59–1.11	ApoE ε4 allele plus basic model
11	0.76	0.64–0.91	0.85	0.59–1.24	ApoE ε4 allele and interaction ApoE ε4 * motivational abilities plus basic model
12	0.79	0.66–0.96	0.90	0.66–1.59	All above covariates

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

Table 3

Hazard Ratio (HR) and 95% CI of Developing MCI and AD by ApoE Genotype

	All participants (n = 2,368)	MCI (n = 313)				AD (n = 71)				
			Basic model[a]		Fully adjusted model[b]			Basic model[a]		Fully adjusted model[b]	
	No. of cases	No. of cases	RR	95% CI	RR	95% CI	No. of cases	RR	95% CI	RR	95% CI
ApoE ε4 carriers[c]	472	76	0.71	0.51–1.00	0.71	0.48–1.04	25	0.67	0.39-1.16	0.48	0.25-0.91
Non-ApoE ε4 carriers[c]	1809	226	0.77	0.64-0.92	0.79	0.65-0.97	46	0.88	0.60-1.31	0.99	0.65-1.53

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

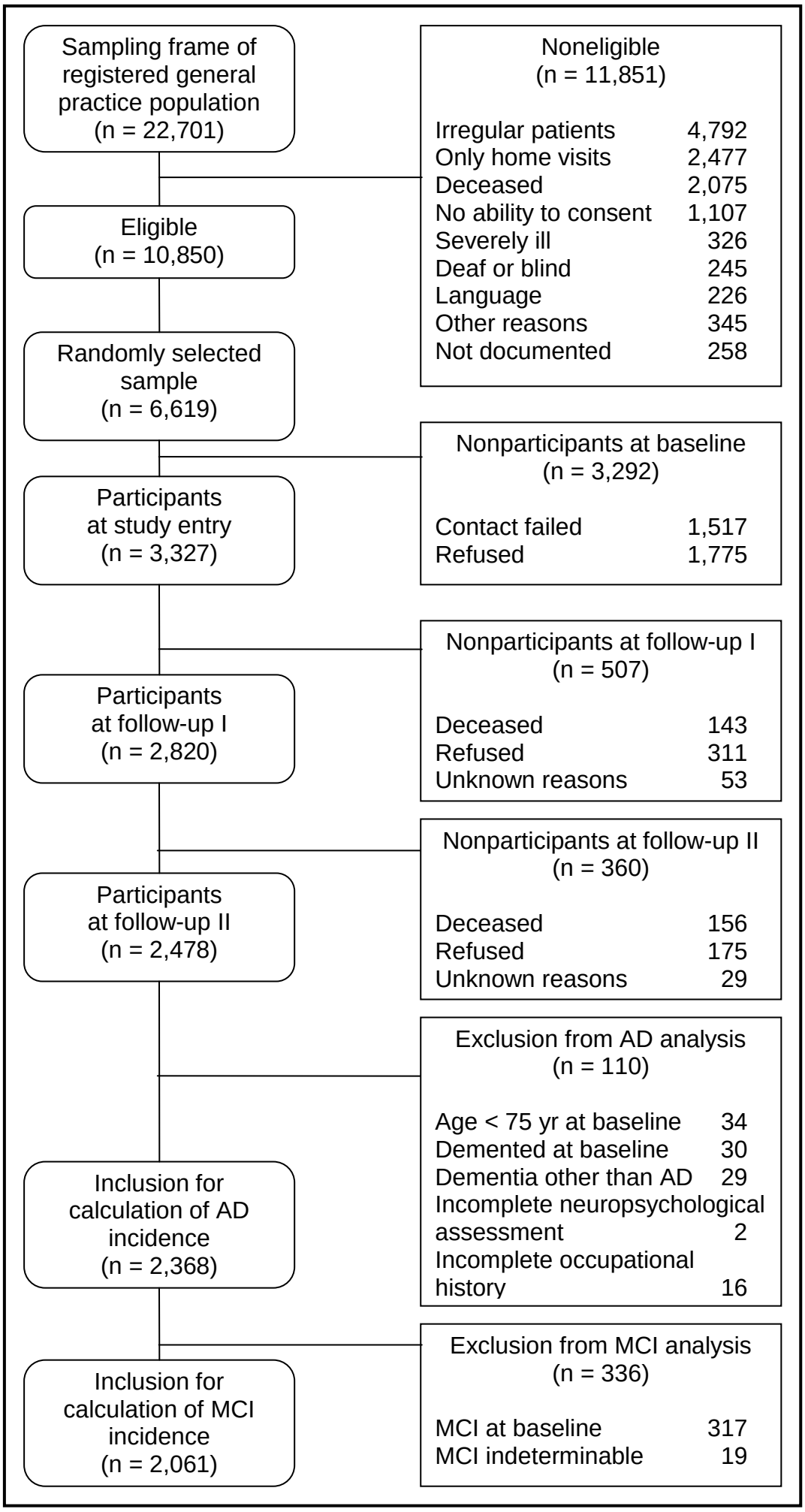
[a] Basic model: Adjusted for age, sex, education, and occupational cognitive abilities.

[b] Fully adjusted model: Adjusted for age, sex, education, occupational cognitive abilities, cognitive functioning at study entry, physical functioning at study entry, cognitive activity, physical activity, family network, vascular risk factors, vascular diseases, depressive symptoms, lifetime depression, and ApoE ε4 allele.

[c] For 87 participants, either DNA was not available or the ApoE genotype could not be determined.

Figure Caption

Figure 1. Flow chart describing sample size.


Sampling frame of registered general practice population (n = 22,701)
Noneligible (n = 11,851)
Irregular patients 4,792
Only home visits 2,477
Deceased 2,075
No ability to consent 1,107
Severely ill 326
Deaf or blind 245
Language 226
Other reasons 345
Not documented 258
Eligible (n = 10,850)
Randomly selected sample (n = 6,619)
Nonparticipants at baseline (n = 3,292)
Contact failed 1,517
Refused 1,775
Participants at study entry (n = 3,327)
Nonparticipants at follow-up I (n = 507)
Deceased 143
Refused 311
Unknown reasons 53
Participants at follow-up I (n = 2,820)
Nonparticipants at follow-up II (n = 360)
Deceased 156
Refused 175
Unknown reasons 29
Participants at follow-up II (n = 2,478)
Exclusion from AD analysis (n = 110)
Age < 75 yr at baseline 34
Demented at baseline 30
Dementia other than AD 29
Incomplete neuropsychological assessment 2
Incomplete occupational history 16
Inclusion for calculation of AD incidence (n = 2,368)
Exclusion from MCI analysis (n = 336)
MCI at baseline 317
MCI indeterminable 19
Inclusion for calculation of MCI incidence (n = 2,061)